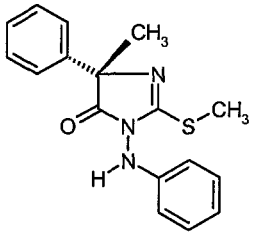
Data Evaluation Report on the aerobic biotransformation of fenamidone in water-sediment system

PMRA Submission Number {.....} EPA MRID Number 45385822

Data Requirement: PMRA Data Code:
EPA DP Barcode: D275213
OECD Data Point:
EPA Guideline: 162-4

Test material:
Common name: Fenamidone
Chemical name
IUPAC: (+)-(4*S*)-4-Methyl-2-methylthio-4-phenyl-(1H)-1-phenylamino-2-imidazolin-5-one.
CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (*S*)-.
CAS No: 161326-34-7.
Synonyms: Reason 500 SC Fungicide.
Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one.
(*S*)-1-Anilino-4-methyl-2-methylthio-4-phenylimidazolin-5-one.
(*S*)-5-Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydroimidazol-4-one.
Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (5*S*)-.
(5*S*)-3,5-Dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-4*H*-imidazol-4-one.
RPA407213.
SMILES string:

Chemical Structure:



Primary Reviewer: Andrew Glucksman
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Company Code: [for PMRA]
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Use Site Category: [for PMRA]

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Signature:
Date:

Company Code: [for PMRA]
Active Code: [for PMRA]
Use Site Category: [for PMRA]
EPA PC Code: 046679

CITATION: Burr, C.M. 1999. [N-Phenyl-U-^{14}C]-RPA 407213: degradation and retention in one water/sediment system. Unpublished study performed by Rhone-Poulenc Agriculture Limited, Essex, UK, and submitted by Aventis CropScience, Research Triangle Park, NC. Laboratory Project ID: 15803. Study experimental start date December 9, 1998, and experimental end date June 19, 1999 (p. 28). Final report issued July 21, 1999.

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Administrative conclusions: This study, conducted with [N-phenyl-U-^{14}C] labeled fenamidone, is classified acceptable and partially satisfies Subdivision N Guideline §162-4 data requirements. This study plus the aerobic aquatic study conducted with [C-phenyl-U-^{14}C]-labeled fenamidone (MRID 45385821) fully satisfy Subdivision N Guideline §162-4.

EXECUTIVE SUMMARY:

The aerobic biotransformation of [N-phenyl-U-^{14}C]-labeled (+)-(4*S*)-4-methyl-2-methylthio-4-phenyl-(1H)-1-phenylamino-2-imidazolin-5-one (fenamidone, RPA407213) was studied in a stream water/sediment system (water pH 6.49, total organic carbon 3.8 ppm; sediment texture loam, pH 7.2, organic carbon 7.3%) for 102 days in the dark under forced air at 20 ± 2°C. [^{14}C]Fenamidone was applied at 0.685-0.734 mg a.i./flask. The sediment/water ratio used was 1:5. The experiment was conducted in accordance with the EU Council Directive 91/414/EEC and according to SETAC, Section 8.2 Aerobic Aquatic Degradation, and in compliance with the OECD-GLP standards. The test system consisted of straight-sided glass flasks attached to traps for the collection of CO_2 and volatile organic compounds. Duplicate samples were collected for analysis after 0.02, 0.25, 1, 2, 7, 14, 30, 61, and 102 days of incubation. The water and sediment phases were separated by decanting. The water samples were analysed directly and also after concentration by freeze-drying. Sediment samples were sequentially extracted with acetonitrile and acetonitrile:water (1:1, v:v) by shaking and Soxhlet. The water, sediment extracts and extracted sediment were analyzed for total radioactivity using LSC. The water and sediment extracts were analysed for [^{14}C]fenamidone and its transformation products by HPLC; peaks were identified by comparison to reference standards. Identifications were confirmed using TLC and LC/MS.

The test conditions outlined in the study protocol were maintained throughout the study; redox potentials of the water and sediment ranged from +7.9 to +227.5 and from -279.5 to -186.6 mV, respectively, during the study.

Overall recoveries of radiolabeled material averaged 95.09 ± 2.41% of the applied with no apparent loss of material. In the water, total [^{14}C]residues decreased from an average 72.68% of the applied at 0.02 days posttreatment to 7.73% at study termination. Extractable [^{14}C]residues in the sediment increased from an average 21.71% of the applied at 0.02 days to a maximum 68.94% at 30 days, and were 58.38% at study termination. Nonextractable [^{14}C]residues in sediment increased from an average 1.12% at 0.02 days to 21.76% at study termination. At the end of the study, an average 5.30% of the applied had been volatilized. No distinction was made between CO_2 and other volatile compounds.

In the entire system, [^{14}C]fenamidone decreased from an average 93.51% of the applied at 0.2 days posttreatment to 55.73% at 102 days. In the water, [^{14}C]fenamidone decreased from 71.80% of the applied at 0.2 days posttreatment to 57.33% at 2 days, 15.43% at 30 days, and 5.04% at 102 days. In the sediment, [^{14}C]fenamidone increased from 21.71% at 0.2 days to a maximum 68.94% at 30 days, then decreased to 50.68% at 102 days. [^{14}C]Fenamidone partitioned quickly from the water to the

sediment; 23% of the fenamidone remaining in the system was associated with the sediment at 0.2 days, 57% at 7 days, and 91% at study termination.

No major transformation products were detected in either the water or sediment. One minor transformation product, RPA405862 (5-methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione), averaged a maximum 2.25% of the applied in the water (102 days posttreatment), 4.18% in the sediment (61 days), and 6.33% in the entire system (102 days). Six to eight unidentified HPLC peaks totaled a maximum 5.20% in the water (14 days) and 11.58% in the sediment (61 days); it was reported that each peak comprised <5.5% of the applied radioactivity.

The reviewer-calculated half-lives for fenamidone in the water and entire system were 14 and 131 days, respectively. The half-life for fenamidone in sediment was not determined because there were only two sampling intervals and a decrease of 17% of the applied after the maximum concentration was measured.

A degradation pathway for [N-phenyl-U-^{14}C]fenamidone was not proposed by the study author. No major transformation products were identified; the majority of residues not identified as fenamidone were associated with the nonextractable fraction.

Results Synopsis:

Test system used: Loam soil flooded with stream water under forced air
Half-life in water (0-30 day): 13.97 days ($r^2 = 0.9307$)
Half-life in sediment: ND.
Half-life in the entire system (0-102 days): 130.78 days ($r^2 = 0.925$)
Major transformation products: No major transformation products were formed.
Minor transformation products:
5-methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione (RPA 405862)

Study Acceptability: This study, conducted with [N-phenyl-U-^{14}C]-labeled fenamidone, is classified acceptable and partially satisfies the Subdivision N Guideline §162-4 data requirements. This study plus the aerobic aquatic study conducted with [C-phenyl-U-^{14}C]-labeled fenamidone (MRID 45385821) fully satisfy Subdivision N Guideline §162-4.

I. MATERIALS AND METHODS

GUIDELINE FOLLOWED: The study was conducted according to the EU Council Directive 91/414/EEC as amended by Commission Directive 95/36/EC of July 1995, Section 7.2.1.3.2, and according to SETAC, Section 8.2 Aerobic Aquatic Degradation, 1995 (pp.12, 68). No significant deviations from USEPA Subdivision N Guideline §162-4 were noted that affect the validity of the study.

COMPLIANCE: This study was conducted in compliance with the OECD Principles of Good Laboratory Practice, as set forth by the United Kingdom Department of Health within the Good Laboratory Practice Regulations 1997 (No. 654 Health and Safety). Signed and dated GLP, Quality Assurance, Certificate of Authenticity, and Data Confidentiality statements were provided (pp. 2-5).

A. MATERIALS:

1. Test Material [N-phenyl-U-^{14}C]fenamidone

Chemical Structure:

Description: Solid (p. 13)

Purity:

[N-Phenyl-U-^{14}C]-labeled: Radiochemical purity: ≥98% (p. 13).
Batch No. PCH 1502
Analytical purity: Not reported.
Initial specific activity: 1.37 GBq/mM.
Final specific activity following dilution with unlabeled fenamidone: 287 Mbq/mM (p. 14).
Location of the radiolabel: Uniformly in the N-phenyl ring

Unlabeled: Analytical Purity: >99.5% (p. 13).
Batch No.: MCD1905.

Storage conditions of test chemicals: The test material was stored in the dark at approximately -20°C (p. 13).

Physico-chemical properties of fenamidone.

Parameter	Details	Comments
Solubility:	7.8 mg/L in water at 20°C. 86.1 g/L in acetonitrile at 20°C.	Data obtained from p. 10, MRID 45385831.
Vapor pressure/volatility:	Not reported.	
UV absorption:	<300 nm	In methanol:pH 7 buffer solution (90:10, v:v; p. 57, MRID 45385830).
pK_a:	Not reported.	
K_{ow}	Not reported.	
Stability at room temperature:	Not reported.	

2. Water collection, storage and properties

Table 1: Description of water-sediment collection and storage.

Description		System 98/38
Geographic location		Unidentified stream, Aldhams Farm, Manningtree, Essex, UK
Pesticide use history at the collection site		Not provided
Collection procedures for	Water:	Collected in large plastic containers
	Sediment:	Not provided
Sampling depth for	Water:	15-20 cm
	Sediment:	Not provided
Storage conditions		In plastic containers (water) or plastic bags (sediment) in the dark at 4°C.
Storage length		Approximately 2 weeks (Table 3, p. 33)
Preparation of water and sediment samples		Water was not filtered. Sediment was sieved (5 mm , then 2 mm) prior to storage.

Data obtained from p. 13 in the study report unless otherwise noted.

Table 2: Properties of the water.

Property	**System 98/38**	
Temperature (°C)	15	
pH	6.49	
Redox potential (mV)	Initial	Final
	+403	+168.8, +227.5
Oxygen concentration (% Saturation)	Initial	Final
	3-54%	94-97%
Dissolved organic carbon (%)	Not provided. Total organic carbon content was 3.8 ppm.	
Hardness (mg/L as $CaCO_3$)	327	
Electrical conductivity	Not provided	
Biomass (mg microbial C/100 g or CFU or other)	Not provided	

Data obtained from Table 2, p. 32 in the study report. Redox potentials and oxygen saturation are for duplicate treated flasks at study termination from Appendix 3, p. 78.

Table 3: Properties of the sediment.

Property	System 98/38	
Textural classification	Loam	
% sand	42.30	
% silt	38.89	
% clay	17.81	
pH in Water in 1M KCl in 0.01M $CaCl_2$	7.2 7.0 7.0	
Organic carbon (%)	7.3	
Organic matter (%)	12.6	
CEC (meq/100 g)	19.5	
Redox potential (mV)	Initial (0.2 days)	Final (102 days)
	-219.9, -238.1	-234.5, -245.3
Bulk density (g/cm^3)	Not provided.	
Biomass (µg C/g) (Measured by the fumigation extraction method. No additional details provided.)	Initial	Final
	248	350

Data obtained from Table 1, p. 31 in the study report. Redox potentials are for duplicate treated flasks at 0 and 152 days posttreatment from Appendix 3, p. 78 in the study report.

B. EXPERIMENTAL DESIGN:

1. Preliminary experiments: No preliminary experiments were conducted.

2. Experimental conditions:

Table 3: Study design.

Criteria	System 98/38
Duration of the test	102 days. Flooded sediment was equilibrated under forced air for approximately 1 month prior to treatment to insure aerobic conditions.
Water: Filtered/unfiltered water: Type and size of filter used, if any:	 Unfiltered stream water Filters were not used

Criteria		System 98/38	
Amount of sediment and water per treatment		Reported to be 56.92 g sediment (dry weight) to 182-250 g water, with the total weight of 433.1-436.7 (Tables 8-10, pp. 38-40).	
Sediment/water ratio		1:5 (as reported by study author, p. 14)	
Application rates (mg a.i./L)		The application rate was not reported in terms of mg a.i./L, but as 0.698 mg a.i/flask for 0.2 day samples, 0.734 mg a.i./flask for the 0.25 day sampled, and 0.685 mg a.i./flask for the remaining samples. At 0.2 days, the measured concentration of [^{14}C]residues in the water was 2.18 mg a.i./L, in the sediment was 2.61 mg a.i./kg, and in the entire system was 1.48 mg a.i./kg.	
Control conditions, if used (present differences from other treatments, i.e., sterile/non-sterile, experimental conditions)		Three sediment/water samples were prepared as described and left untreated. The flasks used for controls had a sidearm attached to the bottom through which a redox probe could be inserted. The samples were maintained as described and used for the determination of pH, oxygen content, and redox potential throughout the study.	
No. of replications	Control, if used	Three	
	Treatments	Duplicate samples were collected at each sampling interval.	
Test apparatus (Type/material/volume)		Sediments were weighed into straight-sided glass conical flask (500 mL, 7.5 cm i.d.), flooded with natural water, and allowed to acclimatize under an aerobic atmosphere at 20 ± 2°C prior to treatment. The test apparatus is illustrated in Figure 1, p.44.	
Details of traps for CO_2 and volatile organics, if any		Humidified air was continuously pumped through the water layer of individual sample flasks, then through one tube of ethylene glycol (30 mL) and two tubes of 2M KOH (30 mL/tube) trapping solutions.	
If no traps were used, is the system closed/open		Volatile traps were used.	
Co-solvent	Identity	Acetonitrile	
	Final concentration	<0.1%	
Test material application	Volume of the test solution used/treatment:	91 µL	
	Application method	Dispensed onto the water surface using a pipette. No mixing occurred.	
Any indication of the test material adsorbing to the walls of the test apparatus?		Not provided	
Microbial biomass/microbial population of the control		Initial	Final
Water		No controls were used.	
Sediment		No controls were used.	

Criteria		System 98/38	
Microbial biomass/microbial population of the treated (µg C/g) Water Sediment		Initial	Final
		Not provided 248	Not provided 350
Experimental conditions:	Temperature (°C)	20 ± 2°C	
	Continuous darkness (Yes/No)	Yes	
Other details, if any		None.	

Data obtained from pp. 14-15 and Table 1, p. 31 in the study report. Application rate data obtained from Tables 8-10, pp. 38-40.

3. Aerobic conditions: Aerobic conditions were maintained in the water phase throughout the study by continually bubbling humidified air through the water layer (p. 15, Figure 1, p. 44). The flow rate was reported to be sufficient to maintain the oxygen content of the water without disturbing the sediment interface. Immediately posttreatment, the redox potential and oxygen saturation of the water ranged from 102.3 to 192.9 mV and 56 to 58%, respectively (Appendix 3, p. 78). The redox potential of the sediment ranged from -238.1 to -219.9 mV.

4. Supplementary experiments: No supplementary experiments were conducted.

5. Sampling:

Table 4: Sampling details.

Criteria	System 98/38
Sampling intervals	0.02, 0.25, 1, 2, 7, 14, 30 61, 102 days
Sampling method	Duplicate flasks were collected at each sampling interval.
Method of collection of CO_2 and volatile organic compounds	Trapping solutions were collected and replaced at each sampling interval.
Sampling intervals/times for: Sterility check, if sterile controls are used: Aerobicity: Water level: pH	 Sterile controls were not used. The redox potential of the treated water and sediment were measured at each sampling interval. Water level in the flasks was monitored, but the addition of water was not needed. The pH of the water phase was measured at each sampling interval.
Sample storage before analysis	The first extraction of sediment was on the day of sampling. The first HPLC analysis was <3 weeks after sampling.
Other observations, if any	None.

Data obtained from pp.16, 19, and Table 3, p. 33 in the study report.

C. ANALYTICAL METHODS:

Separation of the sediment and water: The sediment and water layers were separated by decanting the water into an appropriate container (p. 16). Aliquots of the water were analyzed using LSC.

Extraction/clean up/concentration methods: Water samples collected between 0.2 and 30 days posttreatment were analyzed directly by HPLC and TLC as described below (p. 17). Water samples collected at 61 and 102 days posttreatment were concentrated by freeze drying prior to analysis by LSC and HPLC (p. 19).

Sediment samples were transferred to plastic bottles, extracted twice by mechanically shaking with acetonitrile and once with acetonitrile:water (1:1, v:v; p. 17). After each extraction, the samples were centrifuged and the supernatants decanted. The supernatants (designated "Extract 1") were combined and analyzed for total radioactivity by LSC. Samples from 30 days onward were then Soxhlet-extracted with acetonitrile:water (1;1, v:v) for 20 hours (p. 18). The extract (designated "Extract 2") was analyzed by LSC. Aliquots of Extract 2 were concentrated to dryness using a Turbovap at 35°C (p. 18). The concentrates were made up to volume with acetonitrile and water and analyzed by LSC.

Nonextractable residue determination: Portions of the extracted sediments were analyzed for total radioactivity by LSC following combustion (p. 18). One post-extracted sample (102 days) was

fractioned into humic acid, fulvic acid, and humin fractions using a 0.5 M NaOH extraction procedure (pp. 18-19).

Volatile residue determination: The trapping solutions were analyzed for total radioactivity using LSC (p. 19).

Total ^{14}C measurement: Total radioactivity associated with the samples was determined by summing the radioactivity recovered from the water samples, sediment extracts, extracted sediment, and volatile trapping solutions.

Derivatization method, if used: No derivatization method was utilized.

Identification and quantification of fenamidone: Water and sediment extracts were analyzed by HPLC under the following operating conditions (p. 20): Kromasil KR100-5 C1 column (25 cm × 4.6 mm i.d.); gradient mobile phase combining (A) water:acetonitrile (80:20, v:v), (B) water:acetonitrile (60:40, v:v), and (C) acetonitrile [percent A:B:C (v:v:v) at 0-10 minutes 100:0:0; 10-40 minutes 0:100:0; 40-55 minutes 0:0:100, 55-65 minutes, 100:0:0]; flow rate 1 mL/minute, UV-Vis detection at 230 nm; radioactivity detection using a liquid mixing cell. Column recoveries were >95% of the radioactivity applied to the column (p. 23). Fenamidone was identified by comparison to the retention time of an unlabeled reference standard.

To confirm the identity of fenamidone, selected water samples and sediment extracts (0.2, 2, 7, and 30 days) were analyzed by one-dimensional TLC using silica gel plates developed with ethyl acetate:hexane (65:35, v:v; p. 21., Table 11, p. 41). Radiolabeled compounds were detected using radioimage scanning. Samples were cochromatographed with an unlabeled reference standard, which was visualized using UV light (254 nm). The identification of fenamidone was also confirmed in water and sediment extracts (61 days) using LC/MS in positive ion mode (pp. 21-23).

Identification and quantification of transformation products: Transformation products were quantified and identified by HPLC and TLC as described for fenamidone. Samples were co-chromatographed with the following reference standards (Table 14, p. 41):

Compound	HPLC Relative Retention Time	TLC Typical Rf values
RPA 717879	0.30	Not included.
RPA 408056	0.34	Not included.
RPA 405862	0.60	0.31
RPA 406012	1.07	0.49
RPA 410914	1.23	0.60

Detection limits (LOD, LOQ) for the parent compound: Limits of detection for LSC, HPLC, TLC, and LC/MS analyses were not reported.

Detection limits (LOD, LOQ) for transformation products: Limits of detection for LSC, HPLC, TLC, and LC/MS analyses were not reported.

II. RESULTS AND DISCUSSION:

A. TEST CONDITIONS: During the study, the water layer remained aerobic and the sediment anaerobic, and the system remained biologically active. Redox potentials ranged from +7.9 to +227.5 mV and oxygen saturation from 56 to 97% in the water (Appendix 3, p.78). Redox potentials ranged from -279.5 to -186.6 mV in the sediment. The pH of the water ranged from 6.40 to 8.57. Microbial activity increased slightly from 248 to 350 µg C/g during the 102 days (Table 1, p. 31). It was stated that the incubation temperature was maintained at 20 ± 2°C; however, tabular data were not provided (p. 15).

B. MATERIAL BALANCE: Overall recovery of radiolabeled material averaged 95.09 ± 2.41% of the applied (range 90.96 - 98.67%), with no apparent loss of radioactivity (mean and s.d. calculated by reviewer; Table 4, p. 34).

Table 5: Biotransformation of fenamidone, expressed as percentage of applied radioactivity ((n = 2, mean ± s.d.)), in loam water-sediment systems under aerobic conditions.*

Compound/Test System		Sampling times (days)								
		0.02	0.25	1	2	7	14	30	61	102
Fenamidone (RPA 407213)	Water	71.80	76.62	66.43	57.33	37.38	39.23	15.43	6.57	5.04
	Sediment	21.71	10.20	25.67	34.38	50.00	45.79	67.81	53.44	50.68
RPA 405862	Water	ND	ND	ND	0.18	0.14	ND	0.65	0.68	2.25
	Sediment	ND	ND	ND	ND	ND	1.78	1.13	4.18	4.08
Unidentified radioactivity[1]	Water	0.88	2.03	0.19	1.23	2.83	2.60	1.45	1.33	0.44
	Sediment	ND	ND	0.13	0.39	ND	ND	ND	9.98	3.57
Total volatiles[2]	Entire System	NA	0.01	0.01	0.01	0.21	0.30	1.74	2.77	5.30
Nonextractable residues	Sediment	1.12	3.42	3.86	4.09	5.22	3.46	8.74	15.80	21.76
Total % recovery	Water	72.68	78.64	66.62	58.73	40.35	41.83	17.80	8.58	7.73
	Sediment	22.83	13.62	29.66	38.87	55.22	51.02	77.68	83.45	80.14
	Entire System	95.51	92.27	96.29	97.61	95.78	93.15	97.22	94.81	93.17

* Means without standard deviations were reported by the study author. Entire system data obtained from Table 4, p. 34. Water data obtained from Table 5, p. 35. Sediment data obtained from Table 6, p. 36; total % recovery in the sediment summed from Total Extracts and Unextracted in the sediment in Table 4, p. 34.
1 Reported to consist of up to 8 HPLC peaks in the water, each at <5.5% of the applied, and up to 6 HPLC peaks in the sediment, each at <5% of the applied.
2 No distinction was made between $^{14}CO_2$ and other volatiles except for a statement by the study author that the presence of radioactivity in the KOH traps indicated it was $^{14}CO_2$.
ND Not detected.
NA Not analyzed.

C. TRANSFORMATION OF PARENT COMPOUND: In the entire system, [^{14}C]fenamidone decreased from an average 93.51% of the applied at 0.2 days posttreatment to 55.73% at 102 days (study termination; Table 7, p. 37). In the water, [^{14}C]fenamidone decreased from 71.80% of the applied at 0.2 days posttreatment to 57.33% at 2 days, 15.43% at 30 days, and 5.04% at 102 days (Table 5, p. 35). In the sediment, [^{14}C]fenamidone increased from 21.71% at 0.2 days to a maximum 67.81% at 30 days, then decreased to 50.68% at 102 days (Table 6, p. 36). [^{14}C]Fenamidone partitioned quickly from the water to the sediment; 23% of the fenamidone remaining in the system was associated with the sediment at 0.2 days, 57% at 7 days, and 91% at study termination (calculated by reviewer using data from Tables 5 and 6, pp. 35-36 by summing the fenamidone associated with water and with sediment extracts, then dividing the concentration in the sediment extract by the summed total).

Half-life: Fenamidone dissipated from the water and entire system with reviewer-calculated half-lives of 13.97 and 130.78 days, respectively, using linear regression analysis (Excel 2000). The half-life for fenamidone in sediment was not determined because only two sampling intervals and a decrease of 17% of the applied occurred after the maximum measured concentration. DT50 and DT90 values for fenamidone were calculated by the study author using KIM, a nonlinear two- or three-compartment Schering AG kinetic modeling program that determines time for test substance concentration to decline to 50% and 10% of initial concentration. Of the models tested by the study author, KIM produced the best fit (>-0.96).

Half-life/DT50/DT90 values

Test system	Half-Life			DT50 (days)	DT90 (days)
	Half-life (days)	Regression equation	r^2		
Water phase 0-30 days 0-102 days	 13.97 24.58	Linear form y = mx + b as $lnC = -kt + lnC_0$; lnC_0 is initial concentration (b = y intercept), lnC is concentration at time t (y), k is the slope (m), t is time (x) or $kt = lnC_0 - lnC$. Half-life (t ½) = -(ln 2/k).	 0.9307 0.8883	7.35	56.60
Sediment phase	ND		ND	147.29	ND
Total system	130.78		0.9223	131.36	ND

Data used to calculated the half-lives obtained from Tables 5-7, pp. 35-37 in the study report. DT50 and DT90 data were calculated by the study author using a nonlinear model (Table 12, p. 41).
ND Not determined. Values were not determined because of the extent of the extrapolation.

TRANSFORMATION PRODUCTS: No major transformation products were detected in either the water or sediment. One minor transformation product, RPA405862 (5-methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione), averaged a maximum 2.25% of the applied in the water (102 days posttreatment), 4.18% in the sediment (61 days), and 6.33% in the entire system (102 days; Tables 5-7, pp. 35-37). Six to eight unidentified HPLC peaks totaled a maximum 5.20% in the water (14 days) and 11.58% in the sediment (61 days); it was reported that each peak comprised <5.5% of the applied radioactivity.

NONEXTRACTABLE AND EXTRACTABLE RESIDUES: Extractable [^{14}C]residues in sediment increased from an average 21.71% of the applied at 0.2 days posttreatment to a maximum 68.94% at 30 days and averaged 58.38% at 102 days (Table 4, p. 34). Nonextractable [^{14}C]residues increased from an average 1.12% of the applied at 0.2 days to a maximum 21.76% at 102 days. Organic matter fractionation of one 102-day sediment sample found that 3.37, 5.44, and 9.11% of the applied was associated with the fulvic acid, humic acid, and humin fractions (Table 13, p. 41).

VOLATILIZATION: At the end of the study, an average 5.30% of the applied radioactivity had been volatilized (Table 4, p. 34). The study author suggested that the volatile radioactivity was CO_2 (p. 24); however, no quantitative data distinguishing CO_2 from other volatiles was provided.

TRANSFORMATION PATHWAY:

A degradation pathway for [N-phenyl-U-^{14}C]fenamidone was not proposed by the study author. No major transformation products were identified; the majority of residues not identified as fenamidone were associated with the nonextractable fraction. The study author stated that the predominant transformation product of fenamidone, identified in MRID 45385821 as RPA408056 (5-methyl-2-methylthio-5-phenyl-3,5-dihydroimidazol-4-one) which forms from the loss of the aniline ring, was not detected in this study because of the position of the label (Figure 27, p. 67).

Table 7: Chemical names for identified transformation products of fenamidone

Applicant's Code Name	CAS Number	CAS Chemical Name	Chemical formula	Molecular weight (g/mol)	Smiles string
RPA405862	153969-11-0	IUPAC: 4-Methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione IUPAC: 5-Methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione CAS: 2,4-Imidazolidinedione, 5-methyl-5-phenyl-3-(phenylamino)-		281.3	

D. SUPPLEMENTARY STUDY- RESULTS: No supplementary studies were conducted.

III. STUDY DEFICIENCIES: No deficiencies were identified. This study plus the anaerobic aquatic study conducted with [C-phenyl-U-^{14}C]-labeled fenamidone (MRID 45385821) fully satisfy Subdivision N Guideline §162-4.

IV. REVIEWER'S COMMENTS:

1. In the document *Reduced Risk Rationale for the Use of Fenamidone on Potatoes and Vegetables* (B0003264, no MRID), it is reported that fenamidone is the S-enantiomer compound with none of the R-enantiomer present (p. 16). It is further stated that analysis demonstrated that all of the metabolites of fenamidone that retain the imidazolinone ring are also pure S-enantiomers. No evidence was provided to support this statement.

   The registrant's code numbers used in this MRID do not match the code numbers presented in the *Reduced Risk Rationale*. For example, RPA405862 is RPA410193 and RPA408056 is RPA412708. The reason for the different code numbers was not discussed in any document, but the registrant does note in the *Reduced Risk Rationale* that the racemic mixtures were often

referenced in the original study reports. To avoid confusion, the chemical codes used in each study report are used throughout this DER.

2. The application rate was reported in terms of mg/flask, rather than by volume or weight of the sample. Water was added to the system to bring the depth to 6 cm, rather than being added by volume or weight. In the data tables, the weight of water in each sample is reported to be 182-250 g, the weight of sediment 56.92 g (dry weight), and the weight of the sediment plus water 433.1-436.7 g (Tables 8-10, pp. 38-40). Since the reported weight of the sediment plus water does not equal the sum of the reported weights of sediment and water and the reason for the discrepancy could not be determined, no attempt was made to convert the application data (reported in mg/flask) into mg/L or mg/g.

3. The mean overall recovery for the entire system that was reported by the study author was slightly higher than the mean recovery calculated by the reviewer using Excel 97. It appears that the study author may have used the means of the replicates to calculate overall recovery, while the reviewer averaged the measured value for each sample.

4. The study author suggested that the volatile radioactivity was CO_2 because it was associated with the KOH trapping solutions (p. 24). In the sampling spreadsheets from 102 days, no radioactivity is associated with the ethylene glycol, 2.14% is associated with the first KOH trap, and 0.04% is associated with the second KOH trap (Appendix 6, p. 115). However, there was no indication that the identification of CO_2 in the KOH trapping solution was confirmed by analysis.

5. In the *Reduced Risk Rationale for the Use of Fenamidone on Potatoes and Vegetables* (B0003264, no MRID), it is stated that the maximum proposed per season application rate is 1.07 lb a.i./A (equivalent to 0.54 mg a.i./kg or 0.60 kg a.i/ha). In this study, the application rate was reported to be equivalent to 1551-1662 g a.i./ha (p. 15).

6. Representative HPLC chromatograms presented in Figures 6-15, pp. 47-56 indicated good separation of peaks.

V. REFERENCES

1. Burr, C.M. [C-phenyl-U-^{14}C]-RPA 407213 degradation and retention in two water/sediment systems. Rhone-Poulenc Agriculture Document 201606. 1999.

2. Lynch, M.R. *Ed.* Procedure for assessing the environmental fate and ecotoxicity of pesticides, SETAC, Part 1, Section 8.2, Aerobic Aquatic Degradation. 1995.

3. Light, T.S. Standard solution for redox potential measurements. *Analytical Chemistry*, vol. 44, pp. 1038-1039. 1972.

4. Rowell, D.L. Sediment Science: methods and applications. Addison Wesley Longman, Ltd. 1994.

5. Timme, G., Freshe, H., and Laska, V. *Pflanzenschutz-Nachrichten* Bayer, vol. 39, pp. 187-203. 1986.

6. Burr, C.M. [14C]-RPA 407213 investigation of the chirality of RPA 407213 and major metabolites in animals, plants, sediments and water. Rhone Poulenc Document 201763. In progress.

Attachment 1

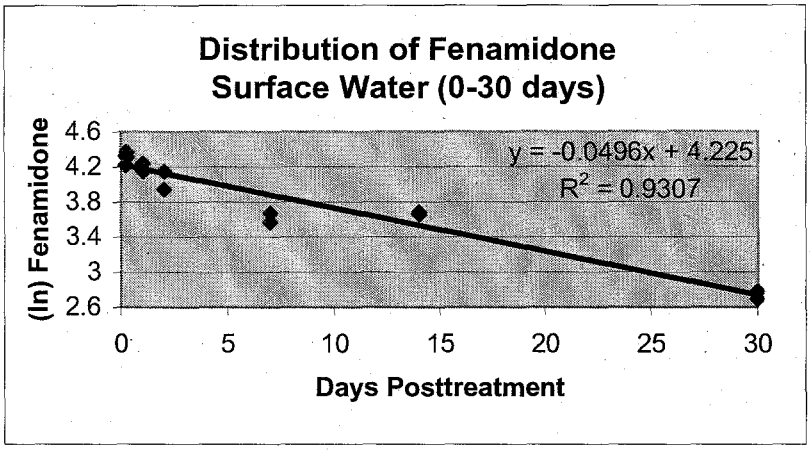
Excel Spreadsheets

Chemical Name: Fenamidone
PC Code: 46679
MRID: 45385822
Guideline No.: 162-4
Soil: loam

Table 5

Half-life:	13.97 Days

Days	% of Fenamidone	ln (% parent)
0.2	67.9	4.217888748
0.2	75.7	4.326910252
0.25	74.4	4.309455942
0.25	78.8	4.367293635
1	63.4	4.149621578
1	69.4	4.24046307
2	63.2	4.145829505
2	51.5	3.941581808
7	35.4	3.566429294
7	39.4	3.672750072
14	39.6	3.679838709
14	38.8	3.658935578
30	14.8	2.693274916
30	16.1	2.778197961

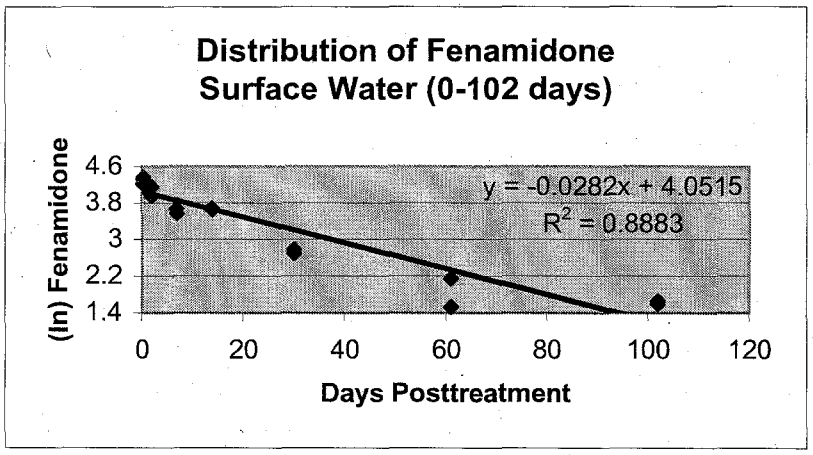


Chemical Name: Fenamidone
PC Code: 46679
MRID: 45385822
Guideline No.: 162-4
Soil: loam

Table 5

Half-life:	24.58 Days

Days	% of Fenamidone	ln (% parent)
0.2	67.9	4.217888748
0.2	75.7	4.326910252
0.25	74.4	4.309455942
0.25	78.8	4.367293635
1	63.4	4.149621578
1	69.4	4.24046307
2	63.2	4.145829505
2	51.5	3.941581808
7	35.4	3.566429294
7	39.4	3.672750072
14	39.6	3.679838709
14	38.8	3.658935578
30	14.8	2.693274916
30	16.1	2.778197961
61	8.5	2.144761008
61	4.6	1.528227857
102	4.9	1.58514522
102	5.2	1.650579856

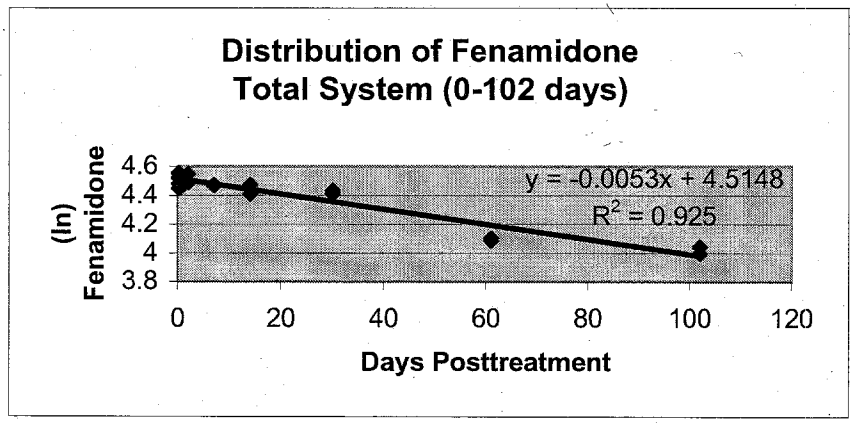


Chemical Name: Fenamidone
PC Code: 46679
MRID: 45385822
Guideline No.: 162-4
Soil: loam

Table 7

Half-life:	130.78 Days

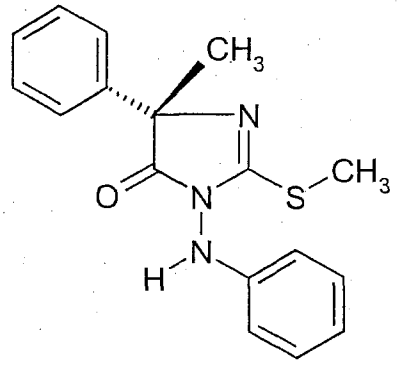
Days	% of Fenamidone	ln (% parent)
0.2	92.1	4.52330916
0.2	94.9	4.552718326
0.25	85.4	4.446760449
0.25	88.3	4.480513581
1	92.6	4.528613063
1	91.6	4.517103707
2	94.3	4.546056921
2	89.2	4.49054466
7	87.5	4.471638793
7	87.3	4.468892168
14	87.8	4.474947599
14	82.2	4.409641802
30	84.1	4.432006567
30	82.4	4.411342689
61	60.5	4.102643365
61	59.5	4.086648356
102	54.5	3.997282849
102	57.0	4.043226691



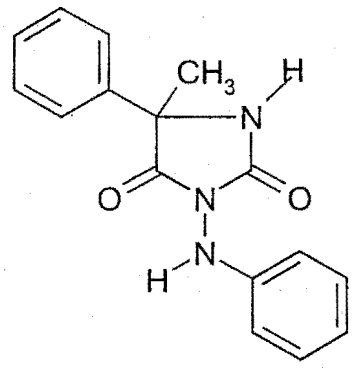
Attachment 2

Structures of Parent and Transformation Products

RPA 407213
IUPAC name: (*S*)-5-Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydroimidazol-4-one
CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (S)-
CAS #: 161326-34-7



RPA 405862
IUPAC name: 5-Methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione
CAS name: 2,4-Imidazolidinedione, 5-methyl-5-phenyl-3-(phenylamino)-
CAS #: 153969-11-0



Attachment 3

Transformation Pathway Presented by Registrant
Illustration of Test System

Figure 27: Proposed Degradation Pathway

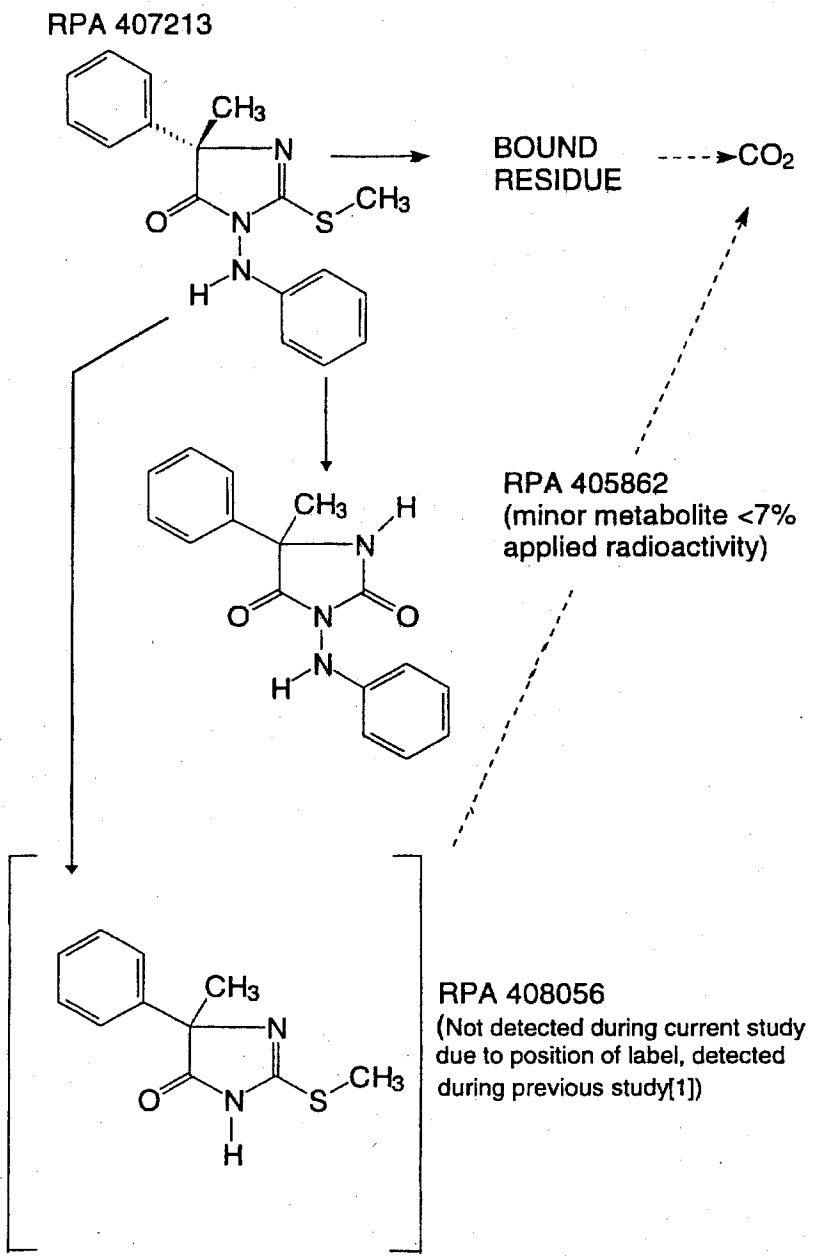


Figure 1: Schematic Diagram of Incubation System

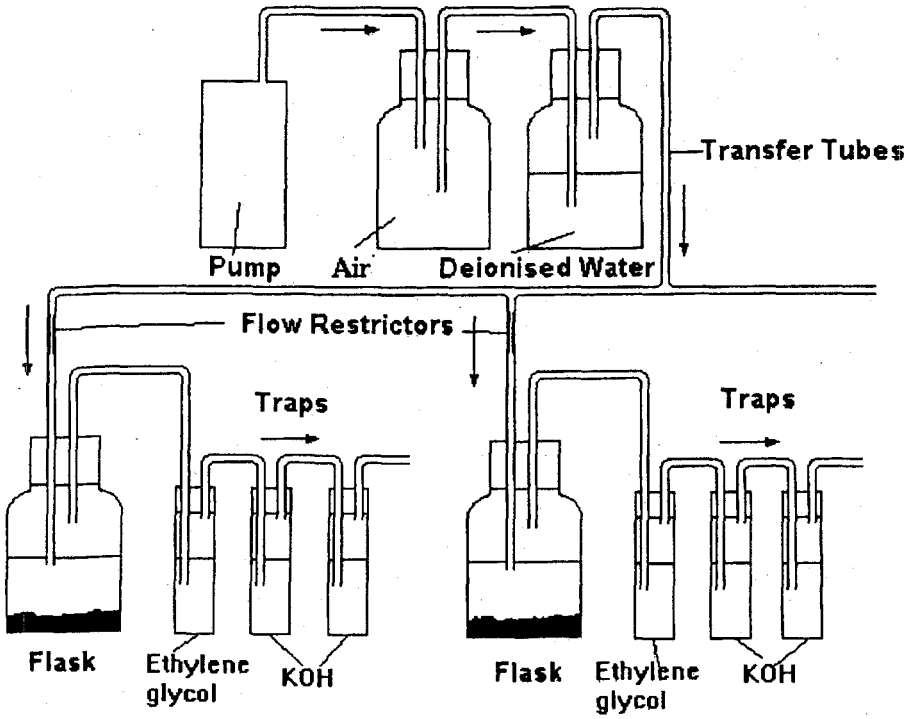


Figure 2: Schematic Diagram of Water Sediment Flask